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Cardiovascular Disease Risk Profiling among First-Degree Relatives of Premature Coronary Artery Disease Patients

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Abstract

Background and Aims: First-degree relatives of patients with premature coronary artery disease are at heightened risk of cardiovascular events due to the synergy of genetic and environmental factors. The aim of this study was to assess the cardiovascular disease (CVD) risk factors and to estimate cardiovascular risk in first-degree relatives of patients with premature CAD.

Methods: The study was conducted among first-degree relatives of patients with coronary artery disease in a tertiary care hospital in Kathmandu. A total of 144 first-degree relatives aged 18 years or older participated in this study. Age and gender matched subjects with no clinical evidence of CAD and no history of premature CAD in first degree relatives were recruited as controls. The cardiovascular risk of study participants was assessed using the American Heart Association (AHA) Cardiovascular Risk Assessment Tool.

Result: The study age group was between 18 to 59 years. The mean age of the subjects was 35.54 ± 10.57 years and 63.19% of subjects were men. A statistically significant number of first-degree relatives of premature CAD were found to be hypertensive and had metabolic syndrome. CVD risk factors like physical inactivity, smoking, diabetes, and dyslipidemia were found in 46.5%, 47.22%, 13.2%, and 52.01%, of the study participants, respectively.

Conclusion: The study highlights the widespread presence of risk factors and underlying medical conditions among young study participants both with and without a family history of premature CAD. Appropriate direction based on opportunistic screening programs and risk stratification should be initiated which can play an important role in the primary prevention of early CAD.

Keywords: Cardiovascular Risk Factors, First-Degree Relatives, Premature Coronary Artery Disease,

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Introduction

Cardiovascular diseases have become a leading cause of morbidity and mortality in adult the population of Indian subcontinent and Nepal is no exception. The trends in CVD mortality and incidence rates have increased between 1990 and 2017.[1]

Although high burden of cardiovascular disease deaths is in itself an adequate reason for attention, a greater cause for concern is the highly malignant form of CAD occurring at an early age in South East Asians.[2] A history of premature maternal and paternal coronary heart disease (CHD) confers a greater risk of CVD than does CHD at older ages.[3] While a positive family history is not modifiable, it can be used to identify individuals in whom a more intensified strategy of prevention by intervening on modifiable risk factors.

The study was conducted in Manmohan Cardiothoracic Vascular and Transplant Center (MCVTC) – a leading referral Center of Nepal for the management of various cardiovascular disorders. The study helps to shed light about risk factor of first-degree relatives of patient with premature CAD.

Methods

The study was single centered, cross sectional, observational study conducted over a period of 12 months during June 2021 to May 2022. The research proposal was approved by the Institutional Review Board (IRB) of the Tribhuvan University, Institute of Medicine. The sample size was calculated with as per the method described by Fleiss.[4] The sample size was calculated with a power of 80% and two-sided confidence level of 95%. The expected prevalence of family history of CVD among control group was considered as 21%.[5] The sample size was calculated to detect a minimum odds ratio (OR) of 2.0 as described in several other studies.[6–8] For a matched study at a case to control ratio of 1:1, the required sample size was 288 with both case and control have 144 case each.

All the first-degree relatives of patients of premature coronary artery disease aged more than 20 years with no history of CAD visiting Manmohan Cardiothoracic Vascular and Transplant Center formed the core of the study population. Age and gender matched subjects with no clinical evidence of CAD and no history of premature CAD in first degree relatives were recruited as controls.

Written consent was obtained, socio-demographic data, behavioral risks and anthropometry and physical parameters were obtained. Blood pressure was measured using doctor's aneroid sphygmomanometer and stethoscope with an appropriately sized cuff on the unclothed left arm. First reading was taken after 15 min rest and second readings were recorded at 10 min interval.Trained technical person collected venous blood, after conforming overnight 12 h fasting to measure blood sugar and lipid profile. Presence of Metabolic syndrome and cardiovascular risk profiling of was done by using National Cholesterol Education Program's Adult Treatment Panel III (ATP III) criteria andACC/AHA risk calculator respectively. Life time ASCVD risk was calculated in cases more than 20 years of age and 10 years ASCVD risk was calculated in cases more than 40 years of age. Ten-year risk for ASCVD is categorized as: Low-risk (<5%) Borderline risk (5% to 7.4%) Intermediate risk (7.5% to 19.9%) and High risk (≥20%)

All the relevant collected data were compiled in a master chart; further statistical analysis of the results was done by computer software devised with statistical package for social service (SPSS) version 20. Categorical variables like gender, obesity status, tobacco use, alcohol was expressed in proportions. Continuous variables like age, blood pressure, blood sugar, lipid profile was given as mean (± standard deviation). The association between two categorical variables was assessed through the use of Chi-square or Fisher's exact test as per the need. Comparison of means between groups was performed by independent t-test. Pearson's correlation analysis was used to compute the association between continuous variables. $P < 0.05$ was considered statistically significant.

CAD was defined as anyone who gives history of significant coronary artery obstruction in angiographic finding or past history of acute coronary syndrome (defined by positive cardiac troponin and at least one of the following: chest discomfort, with persistent or no persistent ST-segment elevation (Electrocardiography(ECG) changes that may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo normalization of T waves; or the ECG may be normal) and imaging evidence of loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.[9] Premature coronary artery disease was defined as any male with coronary artery disease before 55 years of age and 65 years of age for female.[10]

Currently smoking was defined as someone who has smoked more than 100 cigarettes (including hand rolled cigarettes, cigars, cigarillos etc.) in their lifetime and has smoked in the last 28 days.[11] Former smoker was defined as someone who has smoked more than 100 cigarettes in their lifetime but has not smoked in the last 28 days.[11] Never smoked was defined as someone who has not smoked more than 100 cigarettes in their lifetime and does not currently smoke.[11] Total amount of alcohol intake was calculated in a number of the standard drink (10 g of pure ethanol). Average consumption of alcohol of at least one (women) or two (men) standard drinks per day over last 30 days was defined as the excess use of alcohol.[12] Home-brewed alcoholic beverages were classified as distilled (local rakshi) and non-distilled (jaad, chang and tumba). The ethanol concentration of home-brewed alcohol was taken 14.0% for distilled spirits and 5.2% for undistilled spirits.[13]

Insufficient intake of fruit and vegetable was considered if the participants consumed less than five servings (400 g) per day.[14] Physical activities were measured in metabolic equivalents of task (METs) minutes per week. Low level physical activities (physically inactive) were defined as less than 600 MET-minutes per week of physical activities.[12] Weight was divided by square of height (in meters) to calculate Body Mass Index (BMI) of participants. The BMI was classified as underweight (≤18.5 Kg/m^2), normal (18.5–22.9 Kg/m^2), overweight (≥23–24.9 Kg/m^2), and obese (≥25 Kg/m^2).[15] Hypertension was defined as average systolic blood pressure (SBP) ≥ 140 mmHg and/or average diastolic blood pressure (DBP) ≥ 90 mmHg and/or history of taking antihypertensive medication in the last 2 weeks.[16] Diabetes mellitus was defined by the presence of fasting blood sugar ≥126 mg/dl (milligram/deciliter) and/or intake of any anti-diabetic drugs.[17] Dyslipidemia was defined as presence of at least one of the following; raised total cholesterol (≥200 mg/dl), raised triglyceride (≥150 mg/dl), raised low-densitylipoprotein (≥130 mg/dl), decreased high-density lipoprotein (≤40 mg/dl in male and ≤50 mg/ dl in female), and/or use of antilipidemic drugs.

Metabolic Syndrome was defined as anyone having the presence of 3 or more of the following risk factors or on drug to reduce the following risk factor: abdominal obesity (waist circumference ≥90 cm in men and ≥80 cm in women; a high triglyceride level (≥150 mg/dL) or specific medication; a low HDL-cholesterol level (≤40 mg/dL for men and ≤50 mg/dL for women) or specific medication; high blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg or specific medication; and a high fasting plasma glucose concentration (≥100 mg/dL) or specific medication.[18] Anyone with salt intake more than 5gm per day or habit or taking excess salt during daily food intake was labeled to have excess intake of salt.[12]

Result

Among 144 patients 91 (63.19%) were male and 53 (36.81%) females with a male-to- female ratio of 1.7:1. The mean age was 35.54±10.58 years and the range extended from 20 years to 59 years. The mean height and weight of the patients were 160.13 ± 5.61 cm and 60.57 ± 7.81 kg, respectively with a mean Body Mass Index (BMI) of 23.67 ± 2.24 kg/m^2. BMI of majority of the studied population was in category ideal and overweight making 38.9% of studied population. The studies population has statistically significant patient in overweight category.

Table 1.1 Sociodemographic details of the studied population (n = 288)

Variables	Mean ± SD		p-Value
	Case	Control	
Age (years)	35.54 ± 10.58	35.27±10.33	0.86
Weight (kg)	60.57 ± 7.81	60.78±6.71	0.81
Height (cm)	160.13 ± 5.61	160.76±4.79	0.41
BMI (Kg/m^2)	23.67 ± 2.24	23.55±2.65	0.67

Table 1.2 BMI Category of the studied population (n=288)

BMI Category	Frequency		p-Value
	Case	Control	
Underweight	2 (1.4%)	0	0.15
Ideal	56 (38.9%)	73 (50.7%)	0.04
Overweight	56 (38.9%)	35 (24.3%)	0.007
Obese	30 (20.8%)	36 (25%)	0.39
Overweight and Obese	86 (59.72%)	71 (49.31%)	0.07

Among 144 studied cases, 40 (27.8%) were active smokers whereas 28 (19.4%) were former smokers and the rest were nonsmokers. Alcohol intake in moderation was found in 99 (68.8%) cases. Only 55 (38.2%) people consumed a low salt diet. Among all studied cases, adequate physical activity and fruits and vegetable intake was found in 77 (53.5%) and 51 (35.4%) respectively.

Table 1.3 Dietary and Lifestyle of the studied population (n=288)

		Frequency		p-Value
		Case	Control	
Smoking	Current	40 (27.8%)	48 (33.33%)	0.56
	Former	28 (19.4%)	28 (19.4%)	
Alcohol Moderation	Present	99 (68.8%)	89 (61.8%)	0.26
Diet Type	Vegetarian	16 (11.1%)	14 (9.7%)	0.85
	Non-Vegetarian	123(88.9%)	130 (90.3%)	
Low Salt Diet	Yes	55 (38.2%)	47 (32.6%)	0.39
Adequate fruits and vegetable	Yes	51 (35.4%)	44 (30.6%)	0.45
Adequate physical activity	Present	77 (53.5%)	80 (55.6%)	0.81

Table 1.4 Associated diseases of the studied population (n=288)

Cardiovascular Risk Factors	Frequency		p-Value
	Case	Control	
Hypertension	52 (36.11%)	32 (22.22%)	0.009
Diabetes	19(13.2%)	21 (14.58%)	0.84
Dyslipidemia	70 (48.61%)	71 (49.1%)	0.62

Among the studied population more than one third of patient had hypertension which was statistically significant compared to control group. Mean FBS level was 97.37 mg/dl in the studied case population. Mean total cholesterol, HDL, LDL and triglyceride were 177.09 mg/dl, 46.29 mg/dl, 95.09 mg/dl, 149.40 mg/dl respectively. Diabetes and dyslipidemia were found in 19 (13.2%) and 70 (48.61%) of the studied population respectively. The main lipid abnormality consisted of low HDL and high triglyceride in 50 (34.72%) and 51 (35.41%) cases respectively. 20 (12.89%) cases had high LDL level and 25 (17.36%) had high total cholesterol. Among 70 cases of dyslipidemia, 44 were newly diagnosed. Among 26 patients who were on treatment for dyslipidemia 17 were on statins, 6 were on fibrates.

Table 1.5 Lipid abnormalities (n=288)

Lipid Abnormalities	Frequency		p-Value
	Case	Control	
Low HDL	50 (34.72%)	41 (28.47%)	0.25
High triglyceride	51 (35.41%)	45 (31.25%)	0.45
High LDL	20 (12.89%)	19 (13.19%)	0.93
High Total Cholesterol	34 (23.61%)	39 (27.01%)	0.52

Table 1.6 Use of lipid lowering drugs (n=288)

Lipid lowering drugs	Frequency		p-Value
	Case	Control	
None	118(81.94%)	121(84.03%)	0.64
Non pharmacological	3(2.08%)	8 (5.56%)	0.12
Statins	17(11.81%)	11(7.64%)	0.23
Fibrates	6(4.17%)	4 (2.78%)	0.52

In 144 studied cases, metabolic syndrome was found in 48 (33.33%) cases which was statistically significant. In 47 cases with age more than 40 years of age, 10 years ASCVD was calculated in 37 cases, as the calculator does not calculate 10 years risk in cases with LDL level < 70mg/dl. Of 37 cases, 18 (48.65%) had low 10-year ASCVD risk whereas 7(18.92%), 11 (29.73%), 1 (2.7%) had borderline, intermediate and high risk respectively. Compared to control group, the studied population had significantly higher ASCVD risk in population more than 40 years of age.

The mean lifetime ASCD risk score was 43.60 (± 18.32) with minimum 5% and maximum 69%. Nearly half of the studied cases had an ASCVD score more than 50%. Among all cases studied, lifetime ASCVD risk more than 50% in age less than 40 years in was 37 (25.69%) and in age more than 40 years was 35 (34.72%). Though there was no statistically significant lifetime ASCVD risk in patients less than 40 years of age, the risk was more than 50% in one quarter of the studied population. In the studied population of more than 40 years of age there was a significant difference in lifetime ASCVD risk when compared to the control population

Table 1.7 Metabolic syndrome in studied population (n=288)

	Frequency		p-Value
	Case	Control	
Metabolic Syndrome	48 (33.33%)	31 (21.52%)	0.02

Table 1.8: Ten years ASCVD risk in studied population more than 40 years

Category	Frequency		p-Value
	Case (n=37)	Control (n=47)	
Low risk	18 (48.65%)	37 (78.72%)	0.004
Borderline risk	7 (18.92%)	5 (10.63%)	0.28
Intermediate risk	11 (29.73%)	4 (8.51%)	0.01
High risk	1 (2.70%)	1 (2.12%)	0.86

Table 1.9: Lifetime ASCVD risk in studied population (n=288)

Category	Life time ASCVD risk	Frequency		p-Value
		Case	Control	
Age < 40 years	<50%	60 (41.67%)	52 (36.11%)	0.39
	≥50%	7 (25.69%)	43 (29.86%)	0.31
Age > 40 years	<50%	12 (8.33%)	27 (18.75%)	0.004
	≥50%	35 (34.72%)	22 (15.27%)	0.004

Discussion

Total case studied was 144 with male to female ratio of 1.7:1 and mean age 35.54±10.58 years with the range extending from 19 years to 59 years which is comparable to similar studies.[19,20]

The mean Body Mass Index (BMI) of 23.67 ± 2.24 kg/m2 with 38.9% overweight and 20.8% in obese category. In a study conducted by Mittal et al, around 40% of the studied group were either overweight or obese.[20] In a similar study 35% cases were found to have BMI in overweight category.[19] Despite the fact that there are a considerable number of overweight cases among the study participants. Overweight and obese people made up more than 45% of the control group. In a study conducted in Nepal with more than 13,000 participants showed prevalence of overweight or obesity of 31.16%.[21] This rising obesity rates have been observed in a number of emerging nations as a result of rapid urbanization, modernization, and adoption of a lifestyle that involves less physical exercise and higher calorie intake.[17] Easy access to a variety of diets that are high in processed foods, refined carbohydrates, total and saturated fat, and low in fiber has also contributed to rising obesity.

Among the studied population nearly one third had hypertension which was statistically significant. In a similar case control study including first degree relative of premature CAD, there was statistically significant difference in hypertension when compared to control.[22] In a study conducted in Kota, India hypertension was found in 29.7% of all first degree relatives of patient with premature CAD.[20] In another similar study, hypertension was found in 40.8% of all studied cases.[10]

The prevalence of hypertension in 24.4 to 28.4% in various areas of Nepal which slightly lower to our study in which hypertension was found in 32.6%.[16] Twenty five percent of patient in control group also had hypertension. The increase in hypertensive case may be due to increased intake of salt diet, low physical activity and smoking which was found in 61.8%, 46.5% and 27.8% of studied population. The newly diagnosed cases of hypertension were 27.66% of all hypertensive cases. This shows burden of undiagnosed systemic hypertension in the population.

Diabetes was found in 19 (13.2%) out of 144 studied population. Among 19 cases, 5 (26.31%) were newly diagnosed case of diabetes. In study conducted by Subramanyan et al in India, diabetes was found in 11% of study subjects and 22.7% were newly diagnosed cases.[10]

In another similar study done in Iran, first degree relatives of patient with premature CAD, diabetes was found in 6.9% of total studied subjects.[23] This disparity in result may be due to physical inactivity and imbalanced diets. The south Asian population whichhas high tendency for abdominal obesity, excess hepatic fat and, possibly, adverse perinatal and early life nutrition could also be cause of this difference.

The prevalence of diabetes across the provinces in Nepal, is lowest 2% in Province 6 to the highest 10% in Province 3 and Province 4. The prevalence across whole Nepal is 9.2% which is slightly higher in our study.[24] This could be due to the fact that almost half of studied subject had sedentary lifestyle and more than 55% of patient in studied population were either overweight or obese.

Mean total cholesterol, HDL, LDL and triglyceride were 177.09 mg/dl, 46.29 mg/dl, 95.09 mg/dl, 149.40 mg/dl respectively. Among 70 (48.61%) of studied population had at least one abnormality in lipid parameter while performing fasting lipid profile or taking medication for it. The main lipid abnormality consisted of low HDL and high triglyceride in 50 (34.72%) and 43(29.86%) cases respectively. 20 (12.89%) cases had high LDL level and 25 (17.36%) had high total cholesterol. Among 26 patients who had dyslipidemia 17 were on statins, 6 were on fibrates and 3 were on life style modification.

In cross sectional study conducted in Nepal, increased triglyceride level was found in 34.4% of studied population where as high cholesterol level was found in 13.5% which is comparable to our study.[11] In another study done by Mittal et al, high triglyceride was found in 23.5% of studied population and low HDL was found in 39.1%.[20]

The increase in triglyceride and low HDL, which is typically found in patient with metabolic syndrome or diabetes is mainly due to intake of high-calorie, high-fat, and high-sugar diets. Many credible evidence concludes that south Asians are more genetically predisposed to diabetes and have higher levels of insulin resistance which could also have resulted in similar lipid parameter.[17]

In similar study conducted by Saghafi et al, total cholesterol and LDL-C levels were higher than desirable in 36.8% and 15.3% of studied subjects, respectively, 14.6% had lower HDL-C values and 31.9% presented with high triglyceride level. Overall, 60.4% of cases revealed at least one of the lipid abnormalities.[23] The disparity in lipid parameter from our study could be due to increased number of patient with overweight and high number of patient with metabolic syndrome.

Among 144 studied cases, 40 (27.8%) were active smoker whereas 28 (19.4%) were former smoker and rest were nonsmoker. In various similar studies smoking habit was found between 6.9% to 27.7%.[2,16] The data is higher than nationwide non communicable disease (NCD) survey 2013, which was 18.5%.[11]

Alcohol intake in moderation was found in 99 (68.8%) cases. The finding is similar compared to other similar studies, where moderation in alcohol intake or no alcohol intake was found between 74.3 to 83.9%.[2,10] This prevalence is comparable with the results

shown by Sutter et al, where those with paternal history of CHD had a prevalence rate of alcohol use which varied between 10-25%.[22]

Only 55 (38.2%) people consumed low salt diet. Increased salt consumption can be due to using salt/sodium as preservative method, eating pleasure and satisfaction to impart flavor. In STEPS survey conducted in Nepal, around 10% of people admitted to using low salt in diet.[25] Disparity between data between our study and STEPS study may be due to method of calculating salt consumption and recent awareness among people of adverse effect of excess salt intake.

Among all studied cases, adequate physical activity and fruits and vegetable intake was found in 77 (53.5%) and 51 (35.4%) respectively. In a study conducted by Sumesh et al, sedentary life style was present in 22.5% while adequate fruit intake was found in 18.8% of the studied subjects.[2] In another study sedentary life style was present in 38.4% of studied population.[23]

Metabolic syndrome using ATP III criteria was around 33% which is high than Stepwise Approach to Surveillance (STEPS) Survey from Nepal which was done in more than four thousand population and showed metabolic syndrome prevalence of around 15%.[25] This is statistically significant and could be due to shared family habit of sedentary lifestyle and food intake habit in patient with premature CAD. It is also alarming because the presence of metabolic syndrome imparts a high risk of early-onset clinical CAD.[12]

In the study, 10 years ASCVD risk was calculated using ACC ASCVD risk assessment tool. In 47 cases with age more than 40 years of age, 10 years ASCVD was calculated in 37 cases, as the calculator does not calculate 10 years risk in cases with LDL level < 70mg/dl. Of 37 cases, 18 (48.65%) had low 10-year ASCVD risk whereas 7(18.92%), 11 (29.73%), 1 (2.7%) had borderline, intermediate and high risk respectively. When compared to control group first degree relative have significantly high ASCVD risk as computed using ASCVD risk assessment tool. In another similar study comparing risk factor of CAD in first degree premature coronary artery disease high ASCVD risk was found in more than 10% of participants.[2] In study conducted in Nepal with mean age of 53 using WHO/ISH chart proportions of low(<10%), moderate (10-20%) and high CVD risk (>20%) were 86.4%, 9.3%, and 4.3%, respectively.[26] The disparity in result could be due to study done in rural area of Nepal and use of WHO/ISH risk prediction chart instead of ACC ASCVD risk assessment tool.

The study shows more than 40% of cases in borderline and intermediate ASCVD risk group, proper lifestyle modification advice can certainly help these group to prevent further ASCVD risk in future. Similarly, use of coronary calcium score is also necessary in 11 cases to further risk stratify the ASCVD risk and also to see whether there is any indication of statin therapy in these patient according to ACC/AHA cholesterol guideline 2018.[27]

Life time ASCVD risk was also calculated in all 144 studied cases. The mean life time ASCVD risk score was 43.60 (± 18.32) with minimum 5% and maximum 69%. Nearly half of the studied cases had ASCVD score more than 50%. Among all cases studied, lifetime ASCVD risk more than 50% in patient less than 40 years in was 37 (25.69%) and in age more than 40 years was 35 (34.72%).

In study conducted in India, life time ASCVD risk was more than 50% was found in 58% of studied group.[28] In another study conducted in more than 9000 participants, ASCVD risk significantly increases as age advances which was similar to our study result.[29]

There was significantly high ASCVD risk in case more than 40 years of age when compared to control of same age group. The data also highlights increased ASCVD risk in younger study group where life time ASCVD risk was more than 50% is present in one in every four studied cases. The data signifies substantial risk for future cardiovascular event in first degree relative of patient with premature CAD.

Conclusion

The study demonstrates the distribution of potentially modifiable and unmodifiable risk factors among first degree relative of premature CAD patients. A significant number first degree relative were found to be hypertensive and had metabolic syndrome.

The study also shows that first-degree relatives of patients with coronary artery disease have an increased risk burden for cardiovascular disease, as assessed using the ACC risk assessment tool, especially as age advances. An important aspect which this study highlights is the widespread presence of risk factors and underlying medical conditions among young study participants both with and without family history of premature CAD

Appropriate direction based on opportunistic screening programs and risk stratification should be initiated at early age specially in first-degree relatives of patients with premature cardiovascular disease. Therefore, screening for these risk factors in young people in high-risk populations, along with health education, plays an important role in the primary prevention of early CAD, thereby reducing disease burden, morbidity and mortality.

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Conflict of interest **None**

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